MALARIA Prevention and Control

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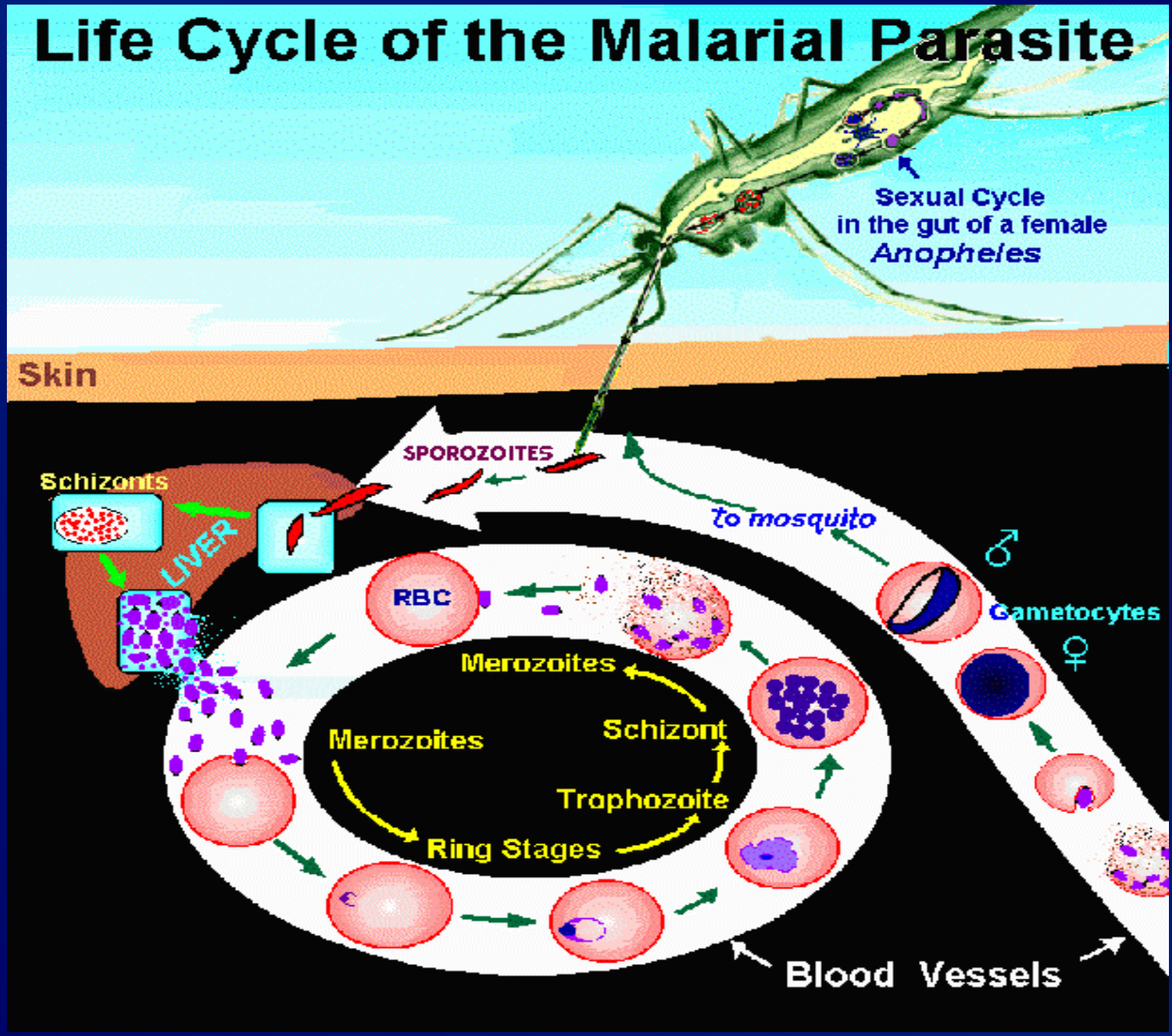
Course Objectives

- Basic understanding of malaria
  - Epidemiology
  - Symptoms
  - Diagnosis
  - Treatment
  - Prevention

What Is It?

- A mosquito-borne infectious disease
- Protozoan parasites of the genus *Plasmodium*
- Transmitted only by Anopheles Mosquitoes
- Disease can be:
  - Acute
  - Chronic
- Four species:
  - *P falciparum*
  - *P vivax*
  - *P ovale*
  - *P malariae*

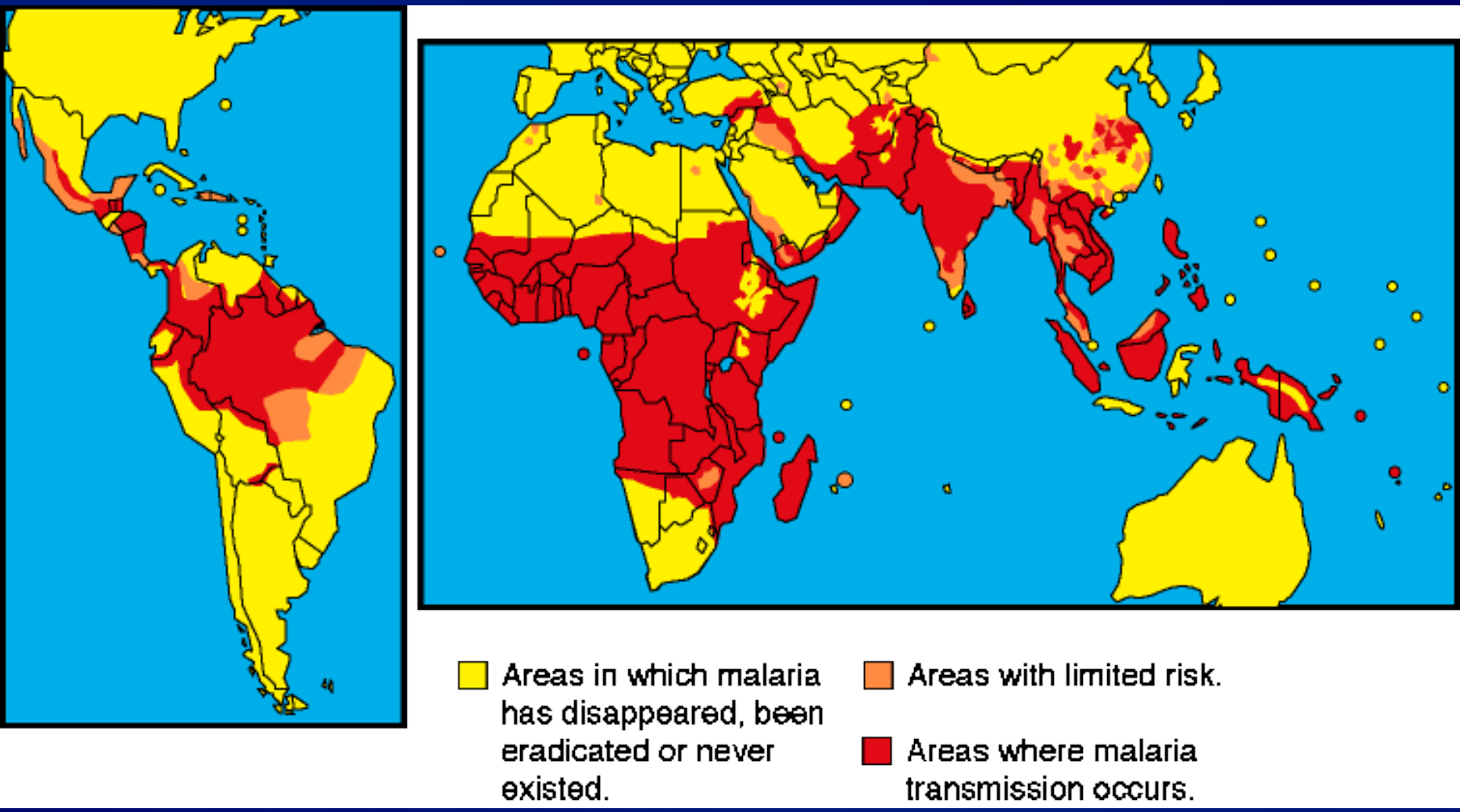

Life Cycle of the Malarial Parasite
Sexual Cycle
in the gut of a female
Anopheles
Skin
SPOROZOITES
Schizonts
LIVER
to mosquito
♂
RBC
Gametocytes
♀
Merozoites
Merozoites
Schizont
Trophozoite
Ring Stages
Blood Vessels

Why The Concern?

- Most prevalent disease in the world
  - 2.1 billion live in MALARIOUS areas
  - 100-300 million new cases annually
  - 1-3 million deaths annually
- Potentially lethal disease
  - January-March 2000: Two U.S. citizens died of malaria after taking inappropriate chemoprophylaxis
- Serious threat to military personnel

July 20, 2001 / 50(28);597-9

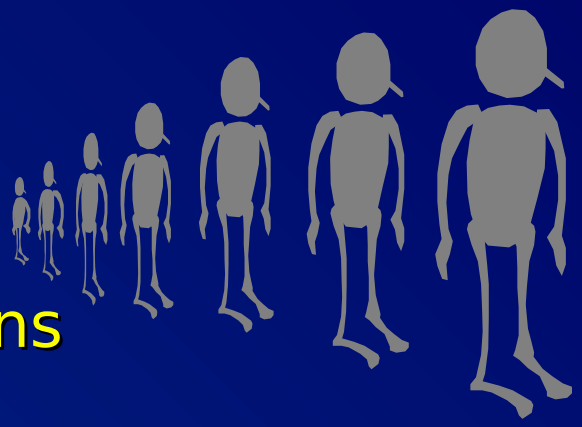
- **Malaria Deaths Following Inappropriate Malaria Chemoprophylaxis**
  - January-March 2000: two U.S. citizens died of malaria due to inappropriate chemoprophylaxis
    - 12 y/o, 3 weeks Nigeria, took chloroquine
    - 47 y/o, 11 days E.. Africa, took chloro/proguanil
  - 4685 cases of malaria in U.S. travelers from 1992 - 2001
  - 893 (19%) inappropriate chemoprophylaxis
  - 2616 (56%) took no chemoprophylaxis
  - Among persons who took inappropriate chemoprophylaxis, 70% took chloroquine for travel to area with known chloroquine resistance (1995 - 2001)


Areas in which malaria has disappeared, been eradicated or never existed.
Areas with limited risk.
Areas where malaria transmission occurs.

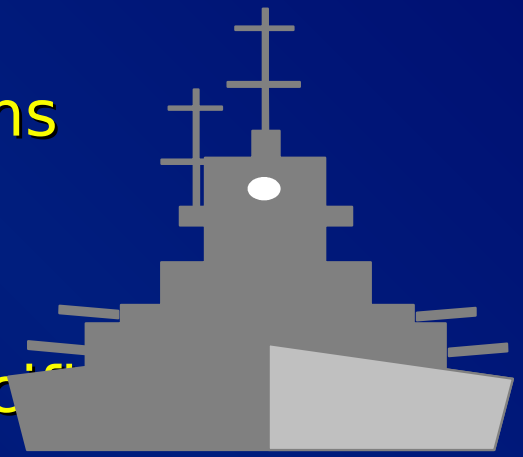
- **AFRICA, ASIA, LATIN AMERICA, CARIBBEAN**
- **Tropics, subtropics, fringes of temperate forests**

Map Source: www.wehi.edu.au/research/infimm/malaria1.html

History



- WWI Naval Forces
  - 4,746 new hospital admissions
  - 68,373 lost man-days
  - 7 deaths
- WWII Naval Forces
  - 111,675 new hospital admissions
  - 3,310,800 lost man-days
  - 90 deaths
  - 5,332 (AVG) daily sick list in pac



History

- Vietnam War Naval Forces
  - 21,695 new admissions
  - 187,478 lost man-days
  - 46 deaths

Recent Historical Experience

- Somalia – 1993
  - 106 Marine, 127 U.S. Army cases
- Sierra Leone –1996
  - 6 Marine, 91 British Army cases
- Navy/Marines
  - 1997-2000 - 62 cases worldwide
- Nigeria – 2001
  - 7 cases with 2 deaths, U.S. Army Special Forces
- Liberia – 2003
  - 80 cases, 71 Marines, 7 Navy, 1 Army, 1 civilian

Transmission

- Man is the only important reservoir
- Vector is female *Anopheles* mosquito
  - Temperature: below 86º F, above 68º F
  - Rainfall: thrive in tropical areas
  - Altitude: rarely exist above 2000 meters
  - Terrain: coastal areas and lowlands with lots of freshwater breeding sites

Transmission

- Mosquito vector: *ANOPHELES*
- Transmission also possible through:

1. Blood transfusion
2. Contaminated needle
3. Organ transplant
4. Congenital

Susceptibility

- Universal susceptibility
- No absolute immunity
  - Partial immunity in areas of high endemicity

Pathogenesis

- RBC destruction
- Immune complexes and mediato
- Capillary permeability
- Tissue hypoxia

Plasmodium Species

- *P. falciparum*
  - Most severe and prevalent
  - 40-60% of cases
  - Widespread CHLOROQUINE resistance
  - Infects RBCs of all ages—Heavy parasitemia
- *P. vivax*
  - 30-40% of cases
  - Liver phase
  - Infects young RBCs: less severe than falciparum
- *P. ovale*
  - Liver phase
  - INFECTS YOUNG RBCs
- *P. malariae*
  - Can persist SUBCLINICALLY for extended periods of time
  - INFECTS OLD RBCs

Incubation Period

- *P. Falciparum* 12 days
- *P. Vivax* 14 days*
- *P. Ovale* 14 days*
- *P. Malariae* 30 days

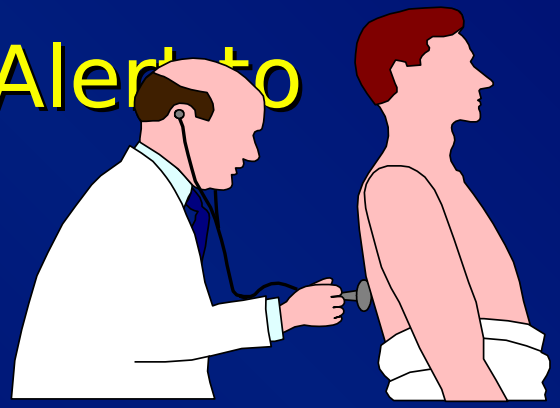
* May be 8 - 10 months or longer for some strains

Presentation

- Fever 96%
- Chills 96%
- Headache 79%
- Muscle Pain 60%
- Palpable liver 33%
- Palpable Spleen 28%
- Nausea or vomiting 23%
- Abdominal pain/diarrhea 6%

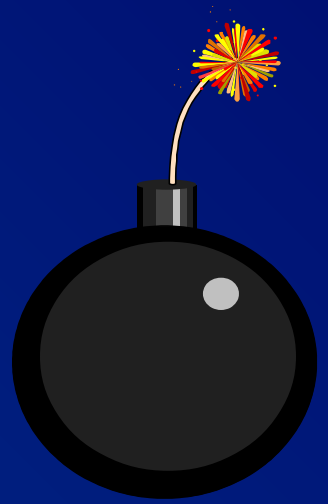
Acute Symptoms & Signs

- Classical cyclic paroxysm:
  - Cold stage: Chills and shaking
  - Hot stage: Warm, headache, vomiting
  - Sweating stage: Weakness
  - Feel well for period of time, then cycle repeats itself
  - Slightly ill to in-distress
- Level of consciousness: Alert to comatose
- Fever



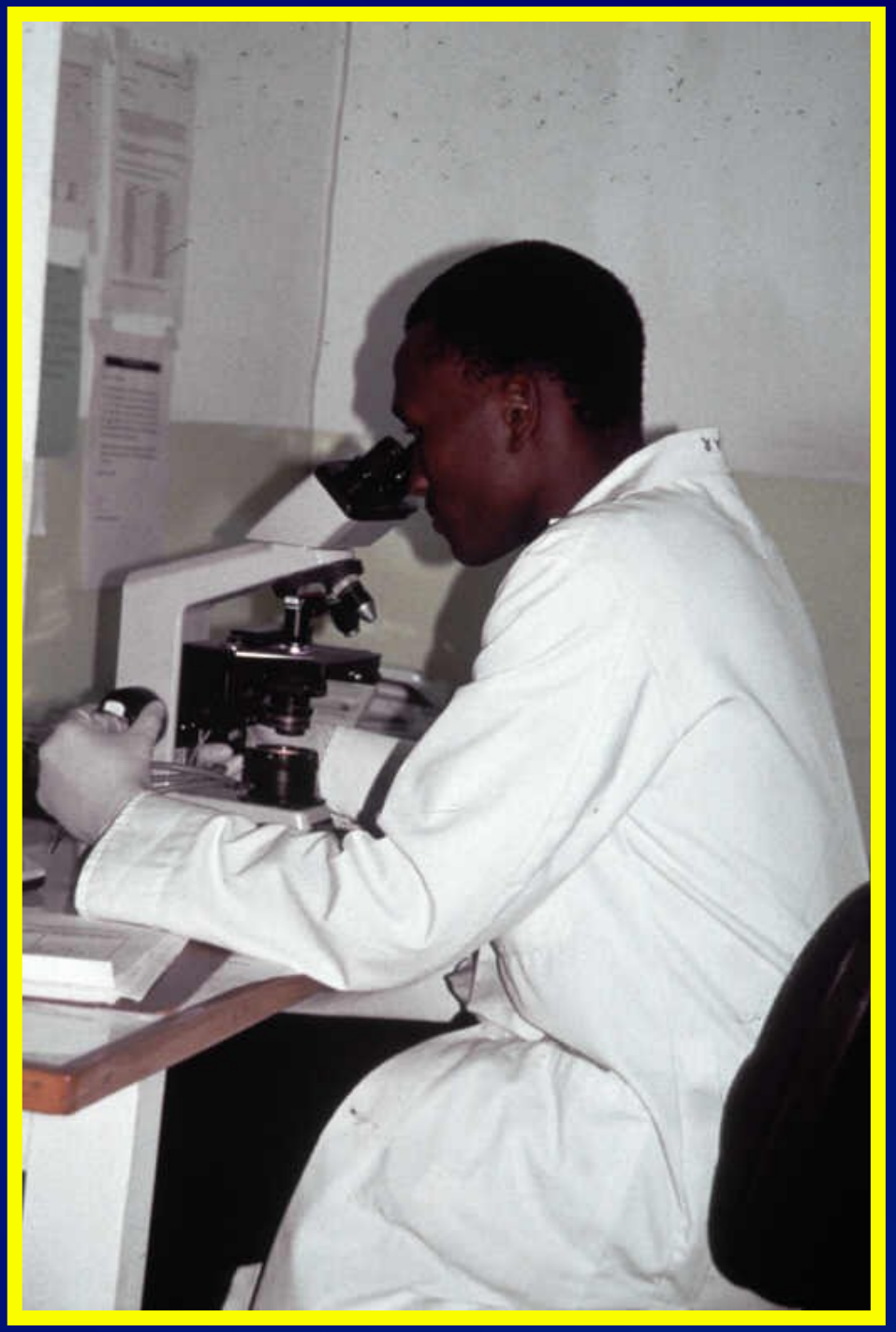
Complicated Malaria

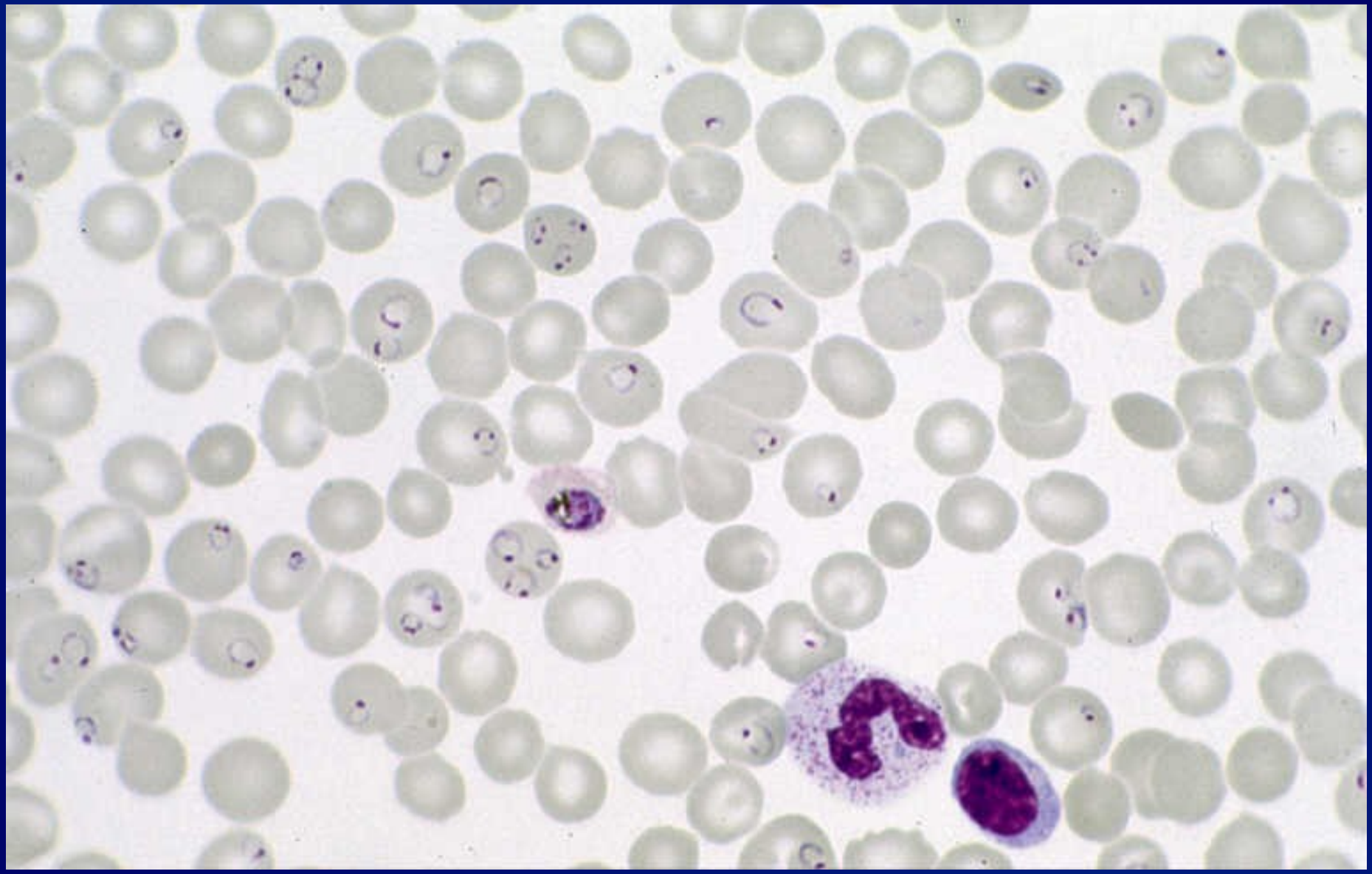
- Hyperparisitemia: (>3%)
- Hypoglycemia: (<60 mg/dl)
- Severe anemia (hct < 21% or rapidly falling hct)
- Renal failure
- Hyponatremia
- Cerebral malaria
- Prolonged hypothermia
- High output vomiting or diarrhea
- Pregnancy



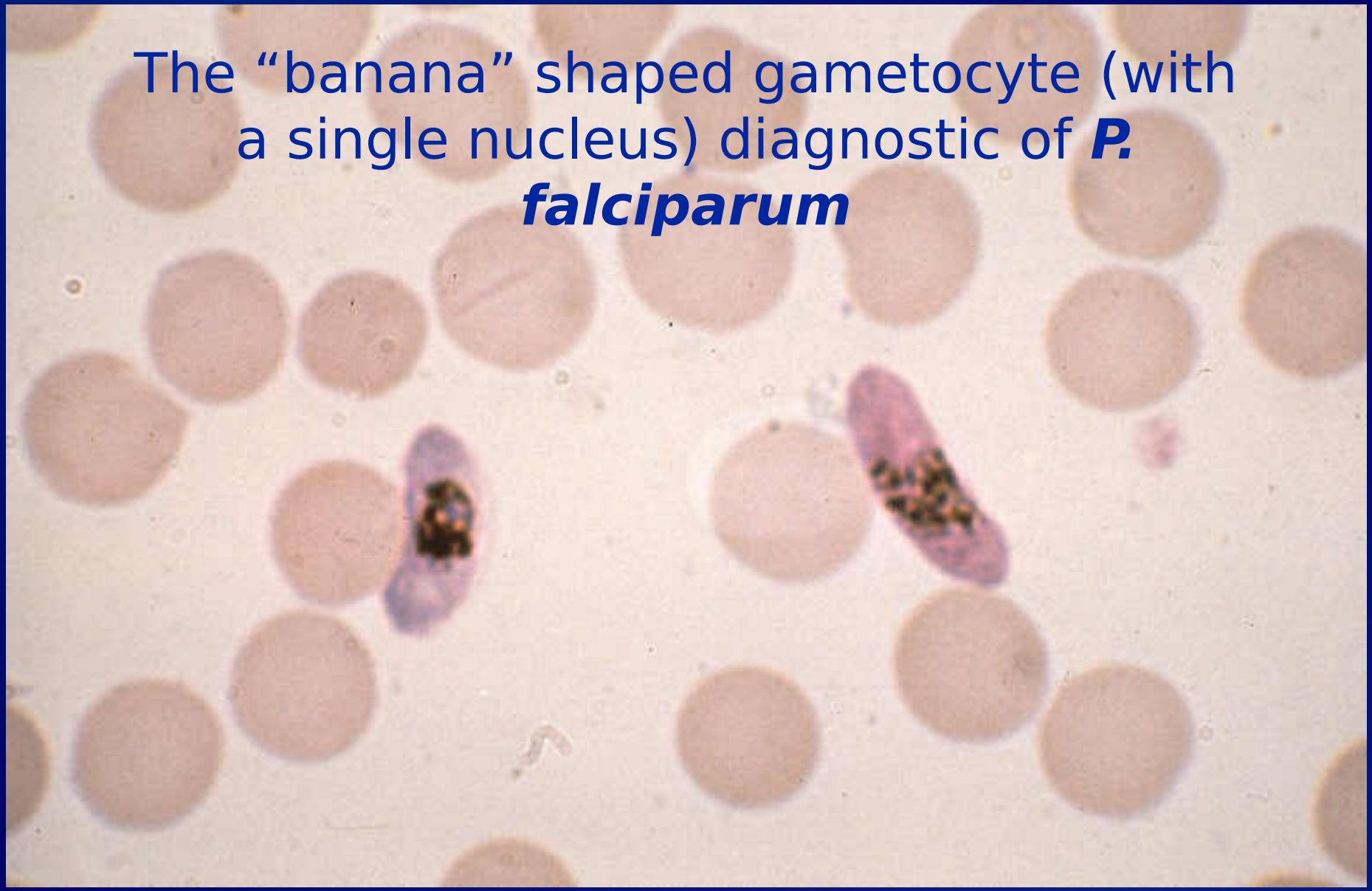
DIAGNOSIS

- **Gold standard: Multiple thick and thin smears**
- **Dip stick tests**
- **CBC**
  - **Anemia**
  - **Leukopenia, or leukocytosis**
  - **No eosinophilia**





The “banana” shaped gametocyte (with a single nucleus) diagnostic of ***P. falciparum***



Treatment

- **CHLOROQUINE sensitive infections:**
  - **CHLOROQUINE 600 mg (2 tabs) P.O. initially**
  - **300 mg (1 tab) in 6 hrs**
  - **300 mg (1 tab) QD for 2 days**

Treatment

- **Uncomplicated CHLOROQUINE-resistant infections:**
  - **Quinine 650 mg PO TID x 3 days and DOXYCYCLINE 100 mg PO bid x 7 days,**

    OR
  - **MEFLOQUINE 1000-1500 mg PO once**

- **Complicated or severe infections**
  - **I.V. QUINIDINE or quinine**

Treatment

- *VIVAX* and *OVALE* therapy should include **PRIMAQUINE** 15mg PO QD x 14 days
- CDC now recommends: **PRIMAQUINE** 30mg PO QD x 14 days

New Antimalarial for Prophylaxis: Atovaquone/Proguanil (*Malarone®*)

- **Licensed July 2000 in USA for treatment and prophylaxis of *P. falciparum***
  - Atovaquone is a blood schizonticide
  - Proguanil is metabolized to cycloguanil, a tissue schizonticide
- **Combination very effective for treatment of multi-drug resistant *P. falciparum***
  - Generally well tolerated with >95% efficacy vs. placebo

Dosage of *Malarone*®

- **Prophylaxis dose: one tablet per day**
- **Start 1-2 days prior to entering endemic area**
- **Continue for one week after leaving**
  - **(causal prophylaxis, kills parasites in liver)**

- **Adult formulation:**
  - **250 / 100 mg atovaquone / proguanil in single combination tablet**
- **Pediatric formulation:**
  - **62.5 / 25 mg single tablet**

Who Should Use *Malarone*® for Prophylaxis?

- Persons on short trips who wish to avoid a long course of medication after return
- Persons concerned about drug side effects
- Persons traveling to areas where resistance to other drugs may occur
- Persons who prefer a daily regimen

Optimal Treatment Approach

- Rapid case identification
- Rapid PARASITOLOGICAL classification
- Rapid initiation of therapy
- Rapid initiation of supportive care

Control of Malaria

- Global eradication efforts attempted by the WHO in 1950s
- Efforts now focus on CONTROL, not eradication

Points Of Attack:

1) Attack the parasite in the human host
2) Reduce contact between humans and mosquitoes
3) Decrease mosquito population

Attack The Parasite In The Human Host

- **Treat malaria infections with effective medications**
- **Use prophylactic drugs to prevent illness and/or infection**

Attack The Parasite In The Human Host

- Chemoprophylaxis is based on current drug resistance patterns
- ***MEFLOQUINE*** first line prophylaxis
  - Mefloquine 250 mg po q week, 1-2 wks prior to 4 wks after
- ***DOXYCYCLINE*** as second line drug
  - Doxy 100 mg po qd, 2 days prior to 4 wks after
- ***PRIMAQUINE***
  - **30 mg*** po qd x 14 days terminal prophylaxis

*15 mg per FDA and drug product information insert

Reduce Contact Between Humans And Mosquitoes

- **Personal protective measures**
  - **Proper wearing of uniform**
  - **DEET**
  - **PERMETHRIN**
  - **Bed nets**

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Decrease Mosquito Population

- Surveillance of mosquito populations
- Identify and eliminate breeding sites
- Proper insecticide application
  - Attack larval stages
  - Attack adult mosquito

Recent and Past Lessons Learned

World War II

Somalia - 1992-3

Liberia - 2003

Lessons Learned: Command Responsibility

- Field Marshall Sir William Slim:

  "If the overall result was less than 95% positive, I sacked the commanding officer. I only had to sack three; by then the rest had got my meaning."

- Sir Neil Cantlie, Dir Gen Brit Army Med Services:

  "When for the first time in history a combatant officer was considered unfit to command a unit on the grounds that he had allowed his men to become ineffective through disease, a new day in military medicine dawned. The clouds of forgetfulness must not be allowed to overshadow the brightness of that day."

Somalia: 1992-3

- 48 cases in country
- 83 cases following return from deployment
  - 62 US Army
  - 21 USMC
- 77% of cases due to *P. vivax*

Somalia Lessons Learned

- Issues
  - Command responsibility
  - Compliance: switch to MEFLOQUINE
  - Location of camps
  - Weather → poor usage of DEET
  - Non-use of bed nets
  - PRIMAQUINE terminal prophylaxis
    - USA had not recommended

Somalia Conclusions

- Cases resulted from failure to implement proper prophylaxis and personal protection
- Mefloquine more effective than Doxycycline in USMC

Conclusions

Education and aggressive monitoring of compliance is needed for chemoprophylaxis and personal protective measures to work

Malaria Outbreak Among Members of JTF Liberia

Consensus Conference Report

9 October 2003

Organizations Represented

- Food and Drug Administration
- Centers for Disease Control and Prevention
- World Health Organization
- Walter Reed Army Institute for Research
- Naval Medical Research Center
- Armed Forces Medical Intelligence Center
- U.S. Air Force Medical Support Agency
- Joint Chiefs of Staff - J4
- Uniformed Services University of the Health Sciences
- Naval Medical Education and Training Command
- DoD Global Emerging Infections System
- Marine Forces, Atlantic
- II Marine Expeditionary Force
- National Naval Medical Center
- Naval Environmental Health Center
- Naval Environmental and Preventive Medicine Unit – Sicily
- Headquarters, Marine Corps, PP&O
- Commander Amphibious Task Force
- Marine Expeditionary Unit 26
- Navy Disease Vector Ecology and Control Center
- Naval Forces Europe
- Joint Task Force - Liberia
- U.S. Army Medical Research and Materiel Command
- U.S. Navy Bureau of Medicine and Surgery
- Headquarters, Marine Corps, Health Services
- U.S. Army Office of the Surgeon General

Background: JTF Liberia Outbreak

- Total of JTF spending any time ashore – 290
  - Quick Reaction Force – 225
  - MEU personnel surveyed during investigation - 157
- 80 cases treated:
  - 51 cases smear positive
  - 29 cases diagnosed by clinical criteria
  - 1 civilian, 1 U.S. Army, 7 U.S. Navy, 2 FAST Marines, 69 Marines of 26th MEU

Background: JTF Liberia Outbreak

- Liberia known to be highest risk area for multiple vector-borne diseases
- AFMIC Risk Assessment for Liberia predicted a malaria attack rate of 11-50% for unprotected personnel
- JTF-L OPORD preventive measures consistent with survey, intelligence and recommendations from AFMIC, CDC and WHO
- Actual Liberia experience:
  - 44% attack rate (69/157) for 26th MEU personnel spending nights ashore
  - 28% attack rate (80/290) for JTF members spending any time ashore

1. Was there a problem with the availability of mefloquine?

- Mefloquine dispensed to Marines
  - Verified by survey
  - Verified by presence of tablets in Marines' pockets upon arrival at NNMC Bethesda
  - Verified by presence of mefloquine in serum samples
- MEU members were taking mefloquine prior to entering Liberia
  - Verified by mefloquine metabolite levels

ANSWER: No. Mefloquine was readily available

2. Was there a problem with the potency or formulation of generic mefloquine?

- Mefloquine met all FDA requirements.
  - Tablets removed from Marines' pockets produced predicted blood levels in test subjects.
  - Chemical analysis by FDA within standards.
  - FDA recommends continued use of current generic mefloquine formulation.

ANSWER: No. Mefloquine potency and formulation was

3. Were Marines taking mefloquine according to requirements?

- Steady-state ratio of mefloquine metabolite (MMQ) present in 93 of 133 indicating past use
- Protective mefloquine (MQ) levels present in 19 of 133 specimens indicating recent use
- Only **7 of 133** had both protective MQ and adequate MQ/MMQ ratio.
  - Inadequate levels noted despite the survey indicating 95% of Marines claimed no missed doses.

ANSWER: No. Lab data indicates inadequate compliance with required

4. Was the malaria parasite resistant to mefloquine?

- Testing at Walter Reed Army Institute for Research did NOT reveal clinically significant resistance
  - Consensus remains that mefloquine is the drug of choice for Liberia

ANSWER: No. Resistance not a factor.

5. Was DEET available for use?

- 290 personnel surveyed.
- DEET use:
  - Possession of DEET was a repeated inspection item.
  - 79/290 (27%) used some type of repellant at least once.
    - Only 19 of these used 12-hour DoD-issued DEET formulation.
  - Majority used less-effective non-DoD supplied or non-DEET repellant.

ANSWER: Yes. Long-acting DEET was available, but not routinely used. Other DEET formulations were more commonly used though less effective as repellants.

6. Were permethrin-treated uniforms available for wear?

- 290 personnel surveyed: 36 (12%) wore permethrin-treated utility uniforms ashore
  - Unable to obtain bulk permethrin for treatment, only aerosol available aboard ship
  - Only desert utilities were treated by aerosol prior to deployment
  - Woodland utilities worn ashore, appropriate to local environment
- Aerosol spray can is the least effective method available for treatment

ANWER: No. Few adequately treated uniforms available for use ashore in Liberia.

7. Were bed nets used?

- Bed nets not carried ashore due to:
  - Weight restrictions
  - No cots to hold poles
  - Sleeping on paved/hard surface precluded pole use
  - Assumed short stay with minimal exposure
- Current issue bed net system requires soft surface for poles or cot to effectively deploy

ANSWER: No. Not used due to net design and mission requirements.

8. Was local insect control adequate?

ANSWER: No. Local control for malaria vectors not feasible given broad distribution, and limited ARG/MEU capabilities.

8. Was local insect control adequate?- Background

- Requirements to analyze and implement insect control exceeded ARG/MEU capabilities
  - Minimal mosquito abatement equipment routinely carried with ARG/MEU
  - No mosquito abatement expertise routinely included in ARG/MEU Table of Organization (T/O)
- Analysis requires:
  - Traps and microscope
  - Expertise to count and identify species
- Site survey following outbreak revealed:
  - Mosquito risk widely and equally spread across region
  - Large local human reservoir of malaria
  - Highly mobile mosquito species, routinely flies > 1 mile to feed

9. Was the medical staff adequately trained in diagnosis and management of malaria?

ANSWER: No. Routine pre-deployment training does not include infectious disease refresher for physicians or lab techs.

9. Was the medical staff adequately trained in diagnosis and management of malaria? - Background

- Recent formal training for one physician, who established initial diagnosis and implemented treatment
- No laboratory technicians had recent formal training
- No formal pre-deployment refresher training received
  - Early diagnosis and treatment decreases morbidity and mortality in malaria
  - Treatment requires medications not used for prophylaxis and not routinely included in AMAL

10. Can U.S. Forces deploy to highly malarious areas, without suffering similar malaria outbreaks?

- Current procedures for personal protective measures effective
- Current chemo-prophylaxis effective
- Currently complex regimen makes implementation difficult

ANSWER: Yes. Present measures, if applied to and by each individual ground force combatant, are adequate to prevent malaria in Liberia and other

Recommendations: Near Term

- Provide USMC-wide guidance requiring:
  - Permethrin treatment for all uniforms and bed nets prior to deployment using best available techniques
  - Use only DoD sustained-release DEET or DEET/Sunscreen formulations
- Provide routine tropical medicine refresher training to MEU medical staff during pre-deployment work-ups
- Add Malarone and oral quinine medications to AMAL
- Operational planners and chain of command emphasize awareness/assessment of infectious disease threat
- Improve training and equipment of ARG/MEU Preventive Medicine technicians to enhance insect control capability

Recommendations: Long-term

- Permethrin treat uniforms at the factory during procurement
- Procure and distribute improved mosquito net system as USMC standard issue
- When OPLANS indicate potential for entry into high malaria-risk area, obtain and assure ARG/MEU capability for continuous onsite assessment and abatement of health threats

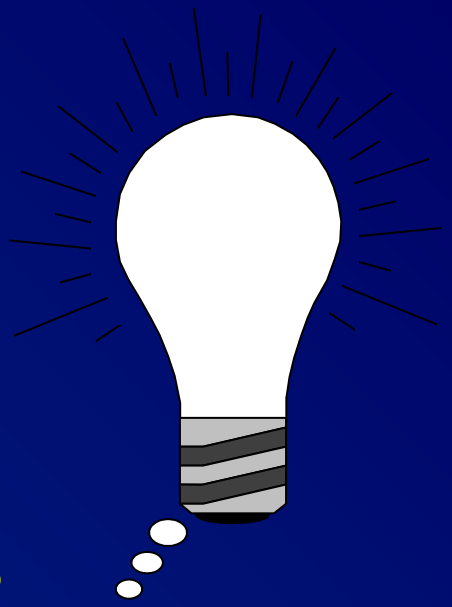
Medical Continuing Efforts

- Malaria antibody testing of blood samples
- Continue ongoing monitoring for emerging permethrin resistance in mosquitoes
- Continue evaluation of malaria parasites for mefloquine resistance

Medical Research and Development

- Field-use malaria test kit
- “Fire-and-forget” solutions to reduce complexity:
  - Support malaria vaccine research
  - Support malaria medication research

Malaria!



- **<u>Remember</u>:**

Flu-like Symptoms

+

‘Recent’ Hx Travel

To Malarious Area

=

<u>Think Malaria</u>

Summary

- Mosquito-borne infectious disease
- Tropics, subtropics
- *P. falciparum, vivax, ovale, malariae*
- Incubation period nearly two weeks
- Cyclic paroxysms
- Fever
- Thick and think blood smears for diagnosis

Summary

- Drug resistance is increasing
- Chemoprophylaxis can prevent infection
- Carefully screen people when prescribing mefloquine
- Great importance of personal protective measures
- Aggressive monitoring needed to enforce ppm at command level
- Regard and manage malaria as medical emergency

Questions?